Cancer Causes and Control 1997, 8, pp. 420-443

Pesticides and cancer

Jan Dich, Shelia Hoar Zahm, Annika Hanberg, and Hans-Olov Adami

(Received 11 June 1996; accepted in revised form 30 October 1996)

Epidemiologic evidence on the relationship between chemical pesticides and cancer is reviewed. In animal studies, many pesticides are carcinogenic, (*e.g.*, organochlorines, creosote, and sulfallate) while others (notably, the organochlorines DDT, chlordane, and lindane) are tumor promoters. Some contaminants in commercial pesticide formulations also may pose a carcinogenic risk. In humans, arsenic compounds and insecticides used occupationally have been classified as carcinogens by the International Agency for Research on Cancer. Human data, however, are limited by the small number of studies that evaluate individual pesticides. Epidemiologic studies, although sometimes contradictory, have linked phenoxy acid herbicides or contaminants in them with soft tissue sarcoma (STS) and malignant lymphoma; organochlorine insecticides are linked with STS, non-Hodgkin's lymphoma (NHL), leukemia, and, less consistently, with cancers of the lung and breast; organophosphorous compounds are linked with NHL and leukemia; and triazine herbicides with ovarian cancer. Few, if any, of these associations can be considered established and causal. Hence, further epidemiologic studies are needed with detailed exposure assessment for individual pesticides, taking into consideration work practices, use of protective equipment, and other measures to reduce risk. *Cancer Causes and Control* 1997, 8, 420-443

Key words: Malignant lymphoma, occupational exposure, soft tissue sarcoma.

Introduction

We describe the international use of pesticides and evaluate the evidence that exposure to pesticides increases the risk of certain cancers in humans. We will provide an overview of extensively used pesticides that are suspected human carcinogens. More detailed information is available in previously published papers, mostly reviews.[1-31] Because the risk of cancer following pesticide exposure from foods appears negligible, this literature was not reviewed. Nevertheless, it is urgent to continue the analytic control of foods and establish maximum allowable levels, particularly when a pesticide is potentially carcinogenic.

A pesticide is defined as any substance or mixture of substances (i) intended for preventing, destroying, or controlling any pest – including vectors of human or animal disease, unwanted species of plants or animals causing harm during the production, processing, storage, transport, or marketing of food, agricultural commodies, wood and wood products, or animal feedstuffs; or (ii) administered to animals for the control of insects, or other pests in or on their bodies.[32-34] The term excludes fertilizers, plant and animal nutrients, food additives, and animal drugs. Agriculture and horticulture, together with vector

Mr Dich is with the Department of Cancer Epidemiology, Institution of Oncology-Pathology, Karolinska Institute and Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden. Dr Zahm is with the Environmental Epidemiology Branch, US National Cancer Institute, Bethesda, MD, USA. Dr Hanberg is with the Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden. D. Adami was with the Department of Epidemiology, University Hospital, Uppsala, Sweden, and is now with the Karolinska Institute, and the Department of Epidemiology and Center for Cancer Prevention, Harvard School of Public Health, Boston, MA, USA. Address correspondence to Mr Dich, Department of Cancer Epidemiology, Institution of Oncology-Pathology, Karolinska Institute and University Hospital, S-171 76 Stockholm, Sweden. *This study was supported by grants from the Swedish Cancer Society.*

control agents in public health programs, account for the most extensive use of pesticides.[35] Significant amounts also are used in forestry and livestock production.

Pesticides can be classified in many different ways; a combined chemical and functional classification is given in Table 1. The chemicals classified differ greatly in mode of action, uptake by and elimination from the body, and toxicity to humans. Pesticides with an extremely high acute toxicity may be easily metabolized and eliminated from the body; following long-term low exposure, they may be less toxic and without carcinogenic or mutagenic properties. On the other hand, pesticides with low acute toxicity – such as organic mercury compounds and some organochlorine compounds – can accumulate in the body and cause chronic toxicity after long-term exposure even in comparatively low doses.

Most commercial pesticide formulations include carrier substances usually mentioned as 'inert ingredients.' Most of them are considered non-toxic, although some are toxic. The adverse effects of the latter, in some instances, may exceed those of the active ingredients. For example, the solvents carbon tetrachloride and chloroform are both toxic to the liver and central nervous system (CNS). Similarly, contaminants in pesticide-formulations include polychlorinated dibenzo-p-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF) in certain phenoxy

Table 1. Pesticides that are suspected human carcinogens, classified by function, chemical subgroup and compound[a]

Main groups	Subgroups	Compounds
Insecticides		
Inorganic		Calcium arsenate
Organic	Organochlorine compounds	Aldrin, dieldrin, chlordane, DDT, HCH, heptachlor, toxaphene
	Organophosphorus compounds	
	Non-systemic	Dichlorvos, (parathion, methyl)[b] (parathion)[b]
	Carbamates	(propoxur)[b]
Specific acaricides		
Non-fungicidal	Organochlorine compounds	(Dicofol)[b]
Protectant fungicides		
Organic	Dithiocarbamates	Thiram
	Phthalimides	Captafol
	Organomercurials	Methylmercury chloride
	Chlorophenols	Pentachlorophenols, 2,4,6-Trichlorophenol
	Others	Chlorothalonil, creosote
Soil fumigants and nematicides		
Soil sterilants		
Fumigant nematicides		Formaldehyde, ethylene dibromide
Non-fumigant nematicides	Carbamates	(carbaryl)[b]
Herbicides		
Inorganic		Sodium arsenite
Organic	Phenolics	Nitrofen
	Phenoxy compounds	2,4-D, 2,4,5-T, MCPA
	Substituted ureas	(diuron),[b] (monuron)[b]
	Triazines	Atrazine
	Dinitroanilines	(trifluralin)[b]
	Others	Amitrol, sulfallate
Plant growth regulators	Carbamates	(chlorpropham),[b] (propham)[b]
Rodenticides		
Fumigants		Methyl bromide
Others	Arsenicals	Sodium arsenite
	Thioureas	Antu

[a] This table is an example of relevant pesticides suspected as human carcinogens by different organizations and is not complete. Important groups like a major subgroup of insecticides such as pyrethroids and anti-fouling products such as tri-butyl tin compounds are not classified as suspect carcinogens by IARC and are not included in the table.

[b] Not classified as suspect human carcinogens by IARC.

acid herbicides (2,4-D, 2,4,5-T), and in wood preservatives, and ethylene thiourea (ETU) in ethylene bis-dithiocarbamate fungicides.

Use and production of pesticides

Historical review[35,36]

Inorganic chemicals, such as arsenic and sulfur, were used to control insects in ancient Greece and Rome. During the sixteenth century, arsenics were adopted as insecticides by the Chinese. Around the turn of the nineteenth century, chemical weed control was demonstrated in France, while in 1913 the first organomercury seed dressings were introduced in Germany. Nicotine from tobacco extracts, pyrethrum, and soap were used for insect control during the nineteenth century, while insects and fungi were combated with a combination of nicotine, sulfur and lime. In the late nineteenth century, the spread of the Colorado beetle was controlled through an impure form of copper arsenite in the United States.

The modern chemical age of pesticides began with the discovery of the insecticidal potential of dichlorodiphenyl trichloroethane (DDT) in 1939 in Switzerland and the development of organophosphorous insecticides in Germany. The commercial production of phenoxy acid herbicides began at the same time in the United Kingdom. The first soil-acting carbamate herbicides were discovered in the UK in 1945 and, simultaneously, the organochlorine insecticide chlordane was introduced in the US and Germany. Many fungicides were introduced during the 1960s and 1970s, *e.g.*, benomyl, and new systemic compounds, such as metalaxyl and triadimefon. During the last 20 years, a better understanding of biological/biochemical mechanisms has resulted in the production of pesticides that are effective at lower doses. A new and important generation of insecticides, for example, comprises synthetic light-stable pyrethroids developed from naturally occurring pyrethrins. New approaches to the design and to methods of application provide an opportunity to reduce the risk of pesticide poisoning, and risk of cancer.

Current use and production

Data on the amount of active ingredient produced are scarce due to the unwillingness of manufacturing companies and their associations to reveal the actual figures. The global sales figures of pesticides are better documented – for example by the World Health Organization (WHO) in collaboration with the United Nations Environment Program[35,37] – as is the transfer of banned pesticides from developed to developing countries.[17] Two recent papers on pesticides in the European Community[38] (EC) and in the Netherlands[39] add valuable information also on the world production.

A wide range of different pesticides have become important in agriculture, mainly in the developed countries, but also increasingly in the developing countries. In the latter, some organochlorine insecticides are still being used, but they are replaced gradually by organophosphorous, carbamate, and pyrethroid insecticides.[40]

The use of pesticides has increased dramatically in both developed and developing countries during the last few decades. With a doubling every 10 years between 1945 and 1985 (Figure 1) about 600,000 tons of pesticides annually are exported to and used in developing countries; about 50,000 of these were used for public health problems. In 1985, the estimated world production of formulated pesticides was three million tons,[35] corresponding to a market value of 15,900 million US dollars.[37] Recent figures from different countries indicate that the use has increased considerably since the early 1980s,

Figure 1. Annual world production in 1,000 metric tons of formulated pesticides, 1945-85. Source: WHO/UNEP, 1990.[35]

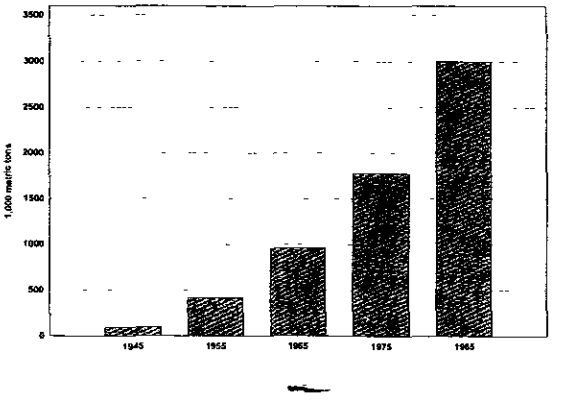


Figure 2. Annual world sales of pesticides by product group in 1,000 metric tons in 1992. Source: Aspelin *et al*, 1992,[41] in Edwards, 1994[40]

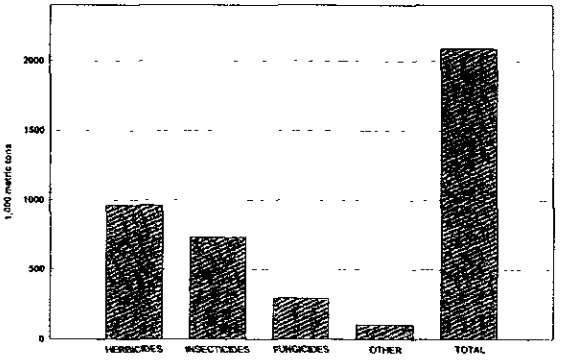


Figure 3. Global production of pesticides by region 1981 and 1990 in 1,000 metric tons of formulated products. Source: United Nations, 1990, in Brouwer *et al*, 1994.[38]

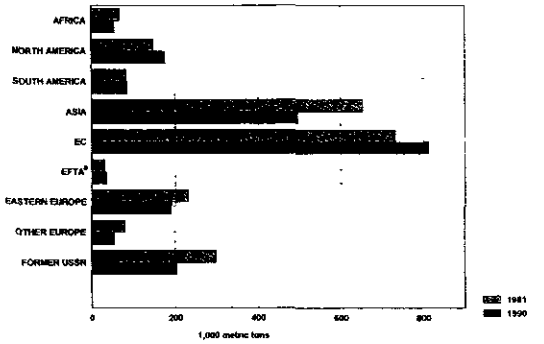
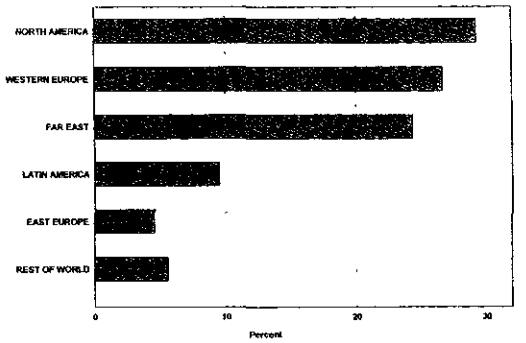


Figure 4. Relative percentage use in tonnage of pesticides in different regions of the world, 1992 Source: Edwards, 1994.[40]



[a] European Free Trade Association: Iceland, Norway, Switzerland (previously with Austria, Finland, Sweden)

except for a small reduction in the early 1990s.[40] In 1991, the global production was estimated to about 2,100 thousand metric tons[41] corresponding to a market value of 25,600 million US dollars.[a] Herbicides constituted 45 percent of the market; insecticides, 30 percent; fungicides, 19 percent; and other pesticides, five percent (Figure 2). The use in the EC in the early 1990s was calculated to be 350,000 tons of active ingredients per year.[38] Since there is a trend to use more selective pesticides, particularly herbicides, actual use compared with calculation of use per acre therefore may be underestimated.

The global production of pesticides by region since 1981 is shown in Figure 3. The use of pesticides is dominating in North America and western Europe (Figure 4). The considerable differences between figures for production and for use in North America depend mostly on differences in the use of formulated products. Some products contain only a few percent of active ingredients and others close to 100 percent. Pesticides banned in the US – such as aldrin, dieldrin, DDT, heptachlor, and chlordane – are exported to developing countries; the amounts are estimated to be considerable.[17,35] For example, DDT has been banned in the US and in most European countries since the 1970s; nevertheless, production and export to countries where they are not banned is estimated to be at record levels.[17] Of about 1,500 chemicals registered for use in pesticide formulations (most of them are not formally evaluated), less than 50 compounds account for about 75 percent of the total use.[42]

Four major vector-borne diseases (malaria, onchocerciasis [river blindness], schistosomiasis and African trypanosomiasis) are controlled by pesticides, such as DDT, dieldrin, and, more recently, endosulfan.[40] Other common vector-borne diseases controlled by organophosphorous insecticides (chlorpyrifos, dichlorvos, fenitrothion, fenthion, malathion, and temephos), but also pyrethrins and pyrethroids include dengue fever, dengue hemorrhagic fever, Japanese encephalitis, South American trypanosomiasis (Chagas disease), leishmaniasis, and louse-borne typhus.[35,43] In some instances, biological methods can control disease vectors.[35,43-45] Insecticides also have been used for treatment of bed nets in tropical countries. Besides ground application, aerial application of pesticides to the bush, to water, and directly to humans can entail considerable individual exposure and contamination of food chains.

Pesticides with large use since the 1950s in both developing and developed countries, are organochlorine compounds, organophosphorous compounds, arsenic- and mercury compounds, phenoxy acid herbicides, atrazine, pyrethroids, and dithiocarbamates.

Animal studies

Carcinogenic pesticides may increase the risk of cancer through a variety of mechanisms, including genotoxicity, tumor promotion, hormonal action, and immunotoxicity. Contrary to genotoxic compounds, carcinogens acting through other mechanisms (tumor promoters) are assumed to have a threshold, *i.e.*, a dose level below which no effects occur. Complete carcinogens have both genotoxic and tumor-promotive potential. Some non-genotoxic pesticides have been evaluated as human carcinogens, *e.g.*, arsenic compounds. In addition, chemicals with weak genotoxicity such as chlordane and 2,3,7,8-

[a] 30,265 million US dollars in 1995, according to the Wood Mackenzie Agrochemical Service

tetrachlorodibenzo-p-dioxin (TCDD) – or with genotoxic effects *in vitro*, but not *in vivo* (such as captafol) – have been evaluated as carcinogenic based on their tumor promotion potential. Atrazine, a genotoxic compound which induces DNA-strand breaks in some cells and increases mammary tumors in rats treated orally (but not in mice) is an example of pesticides that present equivocal evidence of carcinogenicity.

In the US National Cancer Institute (NCI) and the National Toxicology Program (NTP), 47 pesticides have been tested in rats and mice as of 1991, with evidence of carcinogenicity for 23 of them.[46] Of those, 18 also had been evaluated by the International Agency for Research on Cancer (IARC); nine were classified as having 'sufficient' and nine 'limited' evidence of carcinogenicity. The four pesticides not evaluated by IARC, but considered carcinogenic in the NCI/NTP bioassays, are aminotriazole, chloramben, dichloropropene, and piperonyl sulphoxide.[a] Because many old pesticides have been incompletely tested, new documentation often is requested from the manufacturer if there is still need for continuing use of the pesticide. Most countries ban pesticides if there is sufficient evidence of carcinogenicity from occupational exposure in humans. Often, however, evidence of carcinogenicity in animal studies is the main reason for banning a pesticide despite the fact that the amounts tested are at least one or two orders of magnitude higher than the exposure in humans.

Phenoxy acid herbicides do not appear to be genotoxic or carcinogenic in experimental animals, but based on epidemiologic studies, they are classified by IARC as carcinogens with limited evidence of carcinogenicity in humans.

The documentation on the carcinogenicity of DDT and its metabolites in experimental animals is extensive.[1] In mice, the exposure to p,p′-DDT increased the occurrence of hepatoma, of malignant lymphoma (in females)[47] and of leukemia and lung carcinoma.[48] The increase in liver tumor incidence among DDT-exposed animals has been confirmed in many studies.[1] Although IARC considered some studies inadequate, mainly due to short follow-up time, there is yet sufficient evidence of carcinogenicity.

Several organochlorine pesticides (aldrin, benzene hexachloride [BHC], chlordane, chlordecone, DDT, dieldrin, hexachlorobenzene [HCB], heptachlor, lindane and mirex) and contaminants in some pesticides (PCDDs and PCDFs) with estrogenic or antiestrogenic properties recently have been reviewed with respect to carcinogenic properties.[49] The dominating tumor types in rodents exposed to these organochlorines are carcinomas and adenomas of the liver. The compounds reviewed could increase (DDT) or reduce (TCDD) the risk of estrogen-related cancers through hormonal mechanisms, but they also can act through non-hormonal mechanisms. Examples of the IARC evaluations of carcinogenicity from animal and from human studies of the pesticides most widely used and most likely to cause cancer are given in Table 2. In Table 3, all pesticides classified as probably or possibly carcinogenic according to IARC in an overall evaluation of carcinogenicity to humans are listed.

Epidemiologic studies

Ecologic/descriptive studies

Occupational exposure to pesticides in agriculture, horticulture, forestry, and among manufacturers of pesticides and cancer has been studied extensively. No significant increase in overall cancer mortality has been observed among subjects exposed to pesticides.[5,18,21] In most studies, the overall cancer incidence and mortality was lower in farmers, employees in forestry, horticulture, and pesticide applicators than in the general population.[4,6,50-55] However, excess incidence and mortality for several specific cancer sites often have been reported, especially for soft tissue sarcoma (STS), malignant lymphomas (both non-Hodgkin's lymphoma [NHL] and Hodgkin's disease), multiple myeloma, leukemia and cancer of the skin, prostate, testis, lung, and brain.[56,57] In addition, cancers of the breast, endometrium, kidney, liver, bladder, ovary, stomach, and thyroid also have been associated occasionally with pesticide exposure.

General occupational studies in a number of countries have shown elevated risks for some cancer sites among farmers,[3,57,58] and a decreased risk for other sites.[3,58] Correlation studies of county, agricultural practices, and cancer mortality have shown statistically significant excesses of mortality from malignant lymphoma, multiple myeloma, and leukemia following heavy use of insecticides, herbicides, fertilizers, and corn production.[59,60]

Some studies on occupations associated with pesticide exposure have shown excess risk for: NHL[51,57,61-63] and Hodgkin's disease[57,62-64] (but not all[58]); multiple myeloma;[61,65] leukemia;[66] and cancers of the brain and connective tissue,[57] prostate, stomach,[57,61] and testis.[57]

Extensive use of pesticides have been associated with increased incidence of NHL.[67,68] Cancer and other causes of death have been studied in male and female farmers from 23 states in the US.[51] Significant excess risks were observed for prostate cancer in most geographic regions but limited to the central states of the US for NHL, and cancers of the lip, brain, and the lymphatic and hematopoietic system. Nonsignificant excess risks of multiple

[a] Since then, more than 70 pesticides and also intermediate products and impurities in pesticides have been tested and evaluated.[46]

myeloma and leukemia were observed in White women. The mortality from leukemia increased in the Philippines when the use of organochlorine and organophosphorous insecticides increased after adaption of modern rice-cultivation methods in the late 1960s.[13]

Case-control studies

Much of the information on the carcinogenic risk of pesticides comes from case-control studies of selected cancer sites. Exposure assessment was based on occupations involving pesticide exposure, such as farming or forestry, or on the use of individual pesticides. Many, but not all, case-control studies with general occupational data have shown farming and forestry to be associated with excesses of: STS[69-70] (but not all[71]); malignant lymphoma (NHL[61,72-76] [but not all[57,60]] and Hodgkin's disease[77,78]); multiple myeloma;[74,75,78-81] leukemia;[75,82,83] lip cancer;[74,75,83] prostate cancer[74,75,78,83,84] (but not all[85]); and stomach cancer.[75] These studies are limited by their lack of detailed exposure information.

Table 2. Evaluations of carcinogenicity from animal (A) and human (H) studies[a] of common pesticides according to the International Association for Research on Cancer

Compound[b]	Inadequate evidence	Limited evidence	Sufficient evidence
Aldrin	H	A	—
Amitrol	H	—	A
Arsenic, arsenic compounds	—	A	H
Atrazine	H	A	—
Captafol	—	H	A
Chlordane	H	—	A
Chlordecone	—	—	A
Chlorothalonil	—	A	—
Creosote	—	H	A
2,4-D including esters[c]	A	H	—
DDT	H	—	A
1,3-Dichloropropene	H	—	A
Dichlorvos	H	—	A
Dieldrin	H	A	—
Ethylene dibromide	H	—	A
Ethylene oxide	—	H	A
Formaldehyde	—	H	A
Heptachlor	H	—	A
α-HCH	H	—	A
β-HCH	H	A	—
γ-HCH (lindane)	H	A	—
Hexachlorobenzene	H	—	A
Maneb	A,H	—	—
MCPA[c]	—	H	—
Methyl bromide	H	A	—
Methyl mercury chloride	H	—	A
Mirex	—	—	A
Nitrofen	—	—	A
Non-arsenical insecticides	—	A,H	—
Ortho-phenylphenol	—	—	A
Pentachlorophenol	—	H	A
Sodium ortho-phenylphenate	—	—	A
Sulfallate	—	—	A
2,4,5-T-including esters	A	H	—
Thiram	A,H	—	—
Toxaphene (chlorinated camphenes)	—	—	A
2,4,6-Trichlorophenol	—	—	A

[a] Inadequate and limited evidence in humans may be based on only animal studies.
[b] The evaluations apply both to individual chemicals and/or groups of chemicals.
[c] There is no evidence of carcinogenicity in animal experiments according to the World Health Organization.

Table 3. Pesticides and related occupational exposures evaluated as carcinogenic, probably or possibly carcinogenic to humans in the IARC Monographs, Vols. 1–66

Compound	Year	Degree of evidence of carcinogenicity[a]		Overall evaluation of carcinogenicity to humans
		Humans	Animals	
Insecticides				
Aramite®	1987	ND	S	2B
Arsenic and arsenic compounds	1987	S	L	1
Chlordane/heptachlor	1991	I	S	2B
Chlordecone	1987	ND	S	2B
DDT	1991	I	S	2B
Dichlorvos	1991	I	S	2B
Hexachlorocyclohexanes (HCH)	1987	I	—	2B
HCH (techn grade), α-HCH	1987	—	S	—
β-HCH, γ-HCH (lindane)		—	L	—
Mirex	1987	ND	S	2B
Toxaphene (polychlorinated camphenes)	1987	ND	S	2B
Occupational exposure to insecticides	1991	L	—	2A
Fungicides				
Captafol	1991	ND	S	2A
Chlorophenols[b]	1987	L	—	2B
Pentachlorophenol	1991	I	S	2B
2,4,5-Trichlorophenol	1987	—	I	2B
2,4,6-Trichlorophenol	1987	—	S	2B
Hexachlorobenzene	1987	I	S	2B
Ortho-phenyl phenol	1987	ND	S	2B
Sodium ortho-phenylphenate	1987	ND	S	2B
Herbicides			—	
Amitrol	1987	I	S	2B
Atrazine	1991	I	L	2B
Phenoxy acid herbicides[b]	1987	L	—	2B
2,4-D	1987	—	I	—
2,4,5-T	1987	—	I	—
MCPA	1987	—	ND	—
Nitrofen (technical grade)	1987	ND	S	2B
Sulfallate	1987	ND	S	2B
Other				
Creosote[c]	1987	L	S	2A
1,2-Dibromo-3-chloropropane[d]	1987	I	S	2B
Dimethylcarbamoyl chloride[e]	1987	I	S	2A
Ethylene dibromide[d]	1987	I	S	2A
Ethylene oxide[f]	1994	L	S	1
Methyl mercury chloride	1993	I	S	2B

[a] I, inadequate evidence; L, limited evidence; S, sufficient evidence; ND, no data.
[b] This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group.
[c] Wood preservative.
[d] Soil fumigant or nematicide.
[e] Pesticide intermediate
[f] Classified as pesticide (sterilizer for spices) only in some countries.

Herbicides. Studies where cases and controls were queried directly about their use of individual pesticides have produced data on phenoxy acid herbicides, organophosphorous compounds, and triazines. Among forestry workers, farmers, and pesticide applicators and producers, exposure to phenoxy acid herbicides and chlorophenols have been associated with increased risk of STS,[69,70,86-91] NHL,[23,67,92-100] and occasionally with Hodgkin's disease.[93,97] Other studies could not confirm an increased risk for NHL or Hodgkin's disease.[101] In one study, the increased risk for STS appeared due to dioxin-contaminated phenoxy acid herbicides or chlorophenols.[90]

In two nested case-control studies,[91] workers exposed

to phenoxy acid herbicides and their contaminants were at higher relative risk of STS than NHL; the study population included workers with substantial exposure to phenoxy acid herbicides, chlorophenols, and dioxins. These exposures were documented by measurements of serum levels of dioxins, by information on the job and production histories at each plant. The excess risk was not associated specifically with herbicides contaminated with 2,3,7,8-TCDD.

Besides the phenoxy acid herbicides, atrazine is probably the most commonly used herbicide worldwide, used in cultivation of corn, fruit, vegetables, and grapes for producing wine. An association between atrazine and ovarian tumors has been observed in two Italian studies;[102,103] studies in the US[95,98] suggested a weak association with NHL. However, the association did not persist when three case-control studies were combined[104] and adjustment was made for the use of 2,4-D and organophosphorous insecticides

Organochlorine compounds. In a population-based study in Washington State (US), an 80 percent excess risk of NHL was found among those reporting use of DDT.[13] The risk for leukemia rose with frequency of DDT use in a population-based study among White men [105] In a series of Swedish studies, exposure to DDT has been associated with Hodgkin's disease and chronic lymphatic leukemia,[97,106,107] malignant lymphomas,[93] multiple myeloma,[65] and STS[69,87,88] (although one study showed a negative association with STS[90]).

In some studies, DDT and its metabolites have been associated with increased risk of breast cancer.[108,109] However, the largest study published so far,[110] a nested case-control study in which levels of p, p'-DDE were measured in serum sampled several years prior to diagnosis, was negative, and the collective evidence does not support a causal association.[49] One small study[111] has found excess risk of liver cancer associated with DDT.

Exposure to pentachlorophenols usually occurs simultaneously with exposure to other chlorophenols. Several studies,[73,112-114] however, do not support an association with STS, while in one study,[90] exposure to pentachlorophenol more than five years before diagnosis for one week or more was associated with a fourfold excess risk.

Organophosphorous insecticides. Organophosphorous insecticides have been associated with NHL,[115] and in one study,[98] the risks rose with days per year after adjustments for herbicides. Exposure to dichlorvos and other pesticides like nicotine and pyrethrins gave, after a 20-year latency, significant excesses of leukemia.[105]

Wood preservatives (creosotes). Exposure to creosotes – common wood preservatives with somewhat unclear chemical composition mainly based on coal-tar products[12] – have been associated with skin cancer in humans.

Case-control studies published after 1992 are summarized in Table 4.

Cohort studies

Occupations. In several cohort studies[2-5,9,21-24] of farmers, gardeners, forestry workers, paper- and sawmill workers, grain millers and pesticide applicators, overall cancer incidence and mortality was lower than expected. Some recent studies further support these findings. [52,54,55,124]

Among female farmers in Sweden, the cancer incidence also was reduced overall and notably for cancers of the breast and cervix uteri. The standardized incidence ratio (SIR) for NHL was highest in the south of Sweden where the use of pesticides was probably most extensive.[54] Another Swedish study[125] showed an increased risk of NHL among women engaged in animal breeding. An updated Canadian study[99] on farm operators that measured acres sprayed found an excess risk for NHL mortality. Some large cohort studies,[54,55,78,126-8] however, did not observe an excess risk. An increased mortality from multiple myeloma and leukemia was observed in French farmers,[129] while in Italian farmers and agricultural workers an excess risk of stomach cancer was found [52] Most cohort studies found a decreased risk of lung cancer in farmers, agricultural workers, and pesticide applicators.[5,21,51,55,78,127] An excess mortality from lung cancer (about 35 percent) has been found among pesticide applicators in two earlier studies.[130,131] An excess risk of skin cancer has been found in some studies,[5,132] but not in others.[55,78,127] The incidence of prostate cancer is higher in farmers in several,[e.g.,5,133] but not in all studies.[55,128,130] One study indicated an association between number of acres sprayed with herbicides[134] and prostate cancer mortality. A few investigators[135-138] found associations between exposure to pesticides or occupation in agricultural work and testicular cancer, whereas others[55,78,127,139-141] failed to observe that association.

Specific pesticides. Only a few cohort studies provide information on specific pesticides. For example, exposure to carbon disulfide, phosphine, methyl bromide, ethylene dibromide, and DDT – in workers employed in flour mills and employees of the grain elevator department – has been associated with an excess mortality from NHL and leukemia.[142] An increased risk of malignant lymphoma was observed in manufacturers of phenoxy acid herbicides.[143-145] Exposure to phenoxy acid herbicides has been more common in pesticide applicators than in farmers, but no statistically significant increase in the risk of STS or malignant lymphoma was observed.[50]

Table 4. Case-control studies of exposure to pesticides and cancer risk published after 1992

Publication (ref.) Year	Location	Study population	Cancer site	No. of cases	RR[a]	(CI)[b]	Comments
Amadori *et al* [76] 1995	Italy	Farmers and farmer-breeders	NHL including CLL	187	1.8	(1.2-2.6)	Coded on job titles and diagnosed 1988-90. Increased risk for farmers breeding animals, but not for farmers in general.
		Farmers	NHL				
			Low grade	12	1.3	(0.6-2.7)	
			Medium grade	2	0.3	(0.1-1.2)	
			High grade	12	0.8	(0.4-1.6)	
			CLL	5	1 6	(0.5-5.2)	
		Farmer-breeders	NHL				
			Low grade	21	2.2	(1.2-4.3)	
			Medium grade	11	1.7	(0.7-3.4)	
			High grade	19	1.3	(0.7-2.4)	
			CLL	10	3.1	(1 1-8.3)	
Aronson *et al* [84] 1996	Canada	Farming and horticulture					Questionnaire
			Prostate				Pesticides analyzed in partially and fully adjusted models
			< 10 yrs exposure	19	0 8	(0.5-1.4)	
			10+ yrs exposure	33	1.2	(0.8-1.8)	
Bertazzi *et al* [116] 1994	Seveso, Italy	TCDD-exposed general population	All	115	1.0	(0.8-1.2)	Follow-up study until 1986
			Hepato-biliary	10	2.3	(1.2-4.4)	
			NHL	4	1 6	(0.6-4.3)	
			HD	3	2.6	(0.9-9.0)	
			Multiple myeloma	4	3.9	(1.4-17)	
Demers *et al* [81] 1993	US	Agriculture workers:	Multiple myeloma	9	5.2	(1.6-21.1)	High exposure self-reported
		Pesticides > 10 yrs exp.		50	1.3	(1.0-2.2)	
		Farm laborers > 10 yrs exp.		18	1.8	(1.0-4.0)	
Dosemeci *et al* [56] 1994	US	Farmers, farming-related occupations	Prostate	228	1.4	(1.2-1.6.)	African-Americans from 21 states
				891	1.4	(1.3-1.5)	Also from the three southeastern states
Eriksson *et al* [65] 1992	Sweden	Phenoxy acid herbicides	Multiple myeloma	50	2.2	(1 2-4.7)[c]	
		DDT		53	1.8	(1.2-2.6)[c]	
Figgs *et al* [117] 1995	US	Farming, forestry and fishing	NHL	1,152	1.0	(1.0-1 1)	
		Farm workers also identified by 1980 census industry codes		1,130	1.1	(1 0-1.1)	
Franceschi *et al* [71] 1993	Italy	Farmers	Oral cavity & pharynx	78	1.6	(1.2-2.2)	Multi-site study
			STS	8	0.5	(0.2-1.0)	
			NHL	46	0.8	(0.6-1.1)	
			HD	16	1.6	(0 9-2.8)	
			Multiple myeloma	20	1.3	(0.7-2.3)	
			Prostate	42	0.9	(0.6-1.4)	

Continued

Table 4. Continued

Publication (ref.) Year	Location	Study population	Cancer site	No. of cases	RR[a]	(CI)[b]	Comments
Hardell *et al* [118] 1993	Sweden	Dioxin-exposed to all dioxins	STS	352	—	—	Meta-analysis 4 case-control studies
		< 1 yr		58	2.4	(1.7-3.4)	
		1+ yr		24	6.4	(3.5-12)	
		to TCDD		40	3.0	(2 0-4.5)	
		< 1 yr		6	7.2	(2.6-20)	
		1+ yr		18	1.7	(1.0-2.9)	
		to other dioxins		18	6.2	(2.9-13)	
Heineman *et al* [119] 1992	Denmark	Farmers owners	Multiple myeloma	84	1.0	(0.8-1.3)	
		Farmers workers		192	1 1	(0.9-1.3)	
Keller *et al* [83] 1994	US	Farming	Eye[d]	—	6.5	(1.8-23.7)	Patients with other cancers as controls
			Lip[d]	—	4.4	(2.5-7.9)	
			NHL	58	1.1	(0.8-1.5)	
			HD	6	1.2	(0.4-3.5)	
			Multiple myeloma	23	1.3	(0.7-2 3)	
			Prostate	505	1.2	(1.0-1.4)	
			Brain (nervous system)	30	1.4	(0.9-2.2)	
			Leukemia	51	1.5	(1.0-2.3)	
Kogevinas *et al* [91] 1995	International	Production workers	STS	10	10.3	(1.2-90 6)	Two nested case-control studies, exposure to any phenoxy acid herbicide
		Sprayers, 18,390 persons included from 20 cohorts in 10 countries	NHL	19	1.3	(0.5-2.9)	
Pesatori *et al* [120] 1993	Seveso, Italy	TCDD exposure	HD	3	2 0	(0.5-7.6)	Young population in a dioxin-contaminated area
			CLL	2	1.3	(0.3-6.2)	
			Myeloid leukemia	3	2.7	(0.7-11.4)	
			Thyroid	2	4.6	(0.6-32.7)	
Pesatori *et al* [121] 1994	US	Pesticide applicators					Cohort and nested case-control study
		40+ yrs	Lung	38	1.0	—	
		< 40 yrs		22	2.4	(1.0-5.9)	Dead controls
		<10 yrs after license		24	1.0	(0.6-3.3)	Living controls
		10-19 yrs after license		23	1.4	(0.7-3.0)	
		20+ yrs after license		13	2.1	(0.8-5 5)	
		Organochlorine compounds		5	2 6	(0.5-14.3)	Dead controls
Pottern *et al* [122] 1992	Denmark	Women in production of herbicides	Multiple myeloma	363	1.2	(1.0-1 8)	Occupations and industries
		Agricultural production		14	1.5	(0.8-2.8)	
		Orchards		11	1.5	(0.7-3.2)	
		Pesticides		24	1 3	(0.8-2.1)	Possible exposure
		Formaldehyde		56	1.1	(0 8-1.6)	Possible exposure
		Wood products		4	1.1	(0.3-3 4)	Possible exposure

Continued

Table 4. Continued

Publication (ref.) Year	Location	Study population	Cancer site	No. of cases	RR[a]	(CI)[b]	Comments
Richardson *et al*[82] 1992	France		Leukemia	185	—	—	Occupational risks
		Polyvalent farming > 5 yrs		8	4.6	—	
		Insecticides		22	1.7	(1.0-3.1)	
		Total exposure		8	2.1	(0.8-5.4)	
		High or medium exposure					
Siemiatycki *et al*[123] 1994	Canada	Occupations	Bladder	484			
				6	1.2	(0.5-2.9)	Associated to creosote and formaldehyde
				67	1.2	(0.9-1.6)	
Zahm *et al*[104] 1993	US	Farmers	NHL	130	1.4	(1.1-1.8)	Adjusted for age and state
		Atrazine exposure (atrazine, 2,4-D, and organophosphorous compounds)		130	1.2	(0.9-1.7)	Adjusted for age
Zahm *et al*[101] 1993	US	Farmers	NHL	119	1.0	(0.7-1.4)	
		Women: Herbicides		27	0.7	(0.4-1.2)	
		Phenoxy acid		14	0.9	(0.4-1.7)	
		Triazines		12	1.2	(0.6-2.6)	
		Insecticides		56	0.8	(0.5-1.3)	
		Also personally handled		22	1.3	(0.7-2.3)	
		Organophosphorous compounds		14	1.2	(0.6-2.5)	
		Also personally handled		6	4.5	(1.1-17.9)	

[a] RR = relative risks including odds ratios, relative ratios, *etc.*
[b] CI = 95 percent confidence interval.
[c] 90% confidence interval.
[d] No information on number of cases, but probably very few.
Abbreviations used: STS = soft tissue sarcoma; NHL = non-Hodgkin's lymphoma; HD = Hodgkin's disease; CLL = Chronic lymphocytic leukemia.

Occupational exposure to insecticides, *e.g.*, organochlorine insecticides such as DDT combined with others, has been associated with an excess risk of lung cancer,[13,130,133] malignant lymphoma,[4,13,142] multiple myeloma, leukemia, pancreas cancer and skin cancer.[4,13 (rev)] Increased mortality from brain tumors has been observed in some,[133,146,147] but not all studies on pesticide exposure.[148-151] Brain cancer was the only malignancy with a statistically significantly increased standard mortality ratio (SMR) in a cohort study of 2,310 pesticide applicators.[53]

Contaminants in pesticides. A dose-dependent relation with TCDD and all polychlorinated dibenzo-*p*-dioxins and furans (PCDD/F) and death was observed in a cohort comprising 1,189 male workers in a chemical plant in Germany. This plant produced phenoxy acid herbicides, chlorophenols, and other herbicides and insecticides known to be contaminated with TCDD and other higher chlorinated dioxins and furans.[152] The relation of PCDD/F exposure to mortality was investigated by a quantitative estimate of PCDD/F exposure for the whole cohort derived from blood and adipose tissue levels measured in a subgroup of 190 persons.[152]

Exposure to various pesticides, including TCDD-contaminated chemicals, and risk of multiple myeloma have been associated in some studies, but not in others.[21]

Cohort studies published after 1992 are summarized in Table 5.

Discussion and conclusion

General comments. Possible carcinogenic effects of pesticides have been investigated extensively in animal experiments Epidemiologic studies generally have dealt with pesticides as a group. Many studies are hampered by their small size or their design The validity of hospital-based studies is often uncertain and some of them – notably those with cancer patients as controls – were not taken into account. Hence, evidence of excess cancer risk in humans for specific pesticides is lacking, except for arsenic exposure and occupational exposure to insecticides of organochlorine origin. In Tables 2 and 3, we have compared the evaluations from IARC of animal and human studies of pesticides We also have compared the IARC evaluations with the NCI/NTP bioassays and with evaluations from the WHO Environmental Health Criteria.[30] The differences in some evaluations seem to depend mainly on the fact that IARC only evaluates studies published in scientific journals. However, the dominating pesticides suspected as animal and human carcinogens have been evaluated by IARC.

While register linkage studies may provide high statistical power due to their large size, they may be hampered by the crude classification of exposure.[160] Generally, the subjects were classified as being exposed to some undefined mixture of pesticides, and lack of details have prevented assessment of individual pesticides.[67]

Heavy metals

Arsenic and arsenic compounds are the only pesticides classified by IARC as having sufficient evidence of being carcinogenic to humans, based on excesses of lung and skin cancer[13] (Tables 2 and 3). Despite this evidence, arsenic compounds are still used as insecticides in developing countries and as wood preservatives in many developed and developing countries.[40]

Mercury compounds have been used since the beginning of this century as pesticide and seed disinfectants. Following documentation of chronic poisoning by organic mercury compounds in Japan – Minimata, 1953 and Niigata, 1961 – many mercury compounds were banned or withdrawn as pesticides. *Organic mercury compounds* have been associated in some studies with increased risk of brain tumors,[14] an observation which requires confirmation.[53] Following reevaluation of mercury and mercury compounds in 1993, IARC found sufficient evidence that methylmercury is carcinogenic in experimental animals; in humans, the evidence was inadequate. According to the overall evaluation, methylmercury compounds are possibly carcinogenic to humans. However, the use of organic mercury compounds as pesticides has almost ceased; thus, it is more important to study the exposure of inorganic mercury compounds as pesticides.

Herbicides

Phenoxy acid herbicides, in some epidemiologic studies, have been associated with increased risk of STS, malignant lymphoma, and leukemia,[100] but not in others[50,55,114,157] International differences in study results might depend on the type of phenoxy acid herbicides used and the levels of contaminants, mainly 2,3,7,8-TCDD. For example, the phenoxy acid herbicide most commonly used has been 2,4-D in the US, 4-chloro-2-methylphenoxy acetic acid (MCPA) in Sweden , and 2,4,5-T in New Zealand, and contaminants can differ among countries The level of contaminants (TCDD) in 2,4,5-T manufactured in New Zealand was similar to that in Sweden, but no excess risk of STS was found in New Zealand.[161] Two studies in workers exposed to phenoxy acid herbicides, chlorophenols, and dioxins[91] showed excess risk of STS and NHL; this supports earlier findings, but the results might be due to chance. IARC considered the evidence of carcinogenicity to humans as limited and supported mostly by Swedish studies.

Further epidemiologic studies are needed that better account for heterogenicity of diagnosis within the NHL

Table 5. Cohort studies of exposure to pesticides and cancer risk published after 1992

Publication (ref.) Year	Location	Study population	Cancer site[a]	No. of cases	RR[b]	(CI)[c]	Comments
Adami *et al* [49] 1995	Sweden	Retrospective cohort studies TCDD exposure	Breast	24	1.1	(0.7-1.6)	Unexposed excluded. Meta-analysis of international studies
Alavanja *et al* [153] 1994	US	112,000 adult study subjects in agriculture including 42,000 women and pesticide applicators	All, including analyses on: Lung, breast, ovary, colon, stomach, NHL, leukemia, prostate	(ongoing)			Ongoing both cohort and nested case-control studies planned in Iowa and North Carolina in US.
Blair *et al* [78] 1992	US	Farmers	All	65,898	0.9	(0.9-0.9)	Meta-analysis mortality study
			NHL	911	1.1	(1.0-1.1)	8-23 studies
			HD	325	1.2	(1.0-1.3)	
			Multiple myeloma	694	1.1	(1.0-1.2)	
			Leukemia	2,625	1.1	(1.0-1.1)	
			Malignant melanoma	374	1.2	(1.0-1.3)	
			Lip	188	2.1	(1.8-2.4)	
			Skin	348	1.0	(0.9-1.2)	
			Stomach	7,182	1.1	(1.1-1.1)	
			Prostate	7,753	1.1	(1.1-1.1)	
			Testis	161	0.9	(0.8-1.0)	
			Lung	8,018	0.7	(0.6-0.7)	
			Brain	979	1.1	(1.1-1.1)	
Dich *et al* [141] 1996	Sweden	Pesticide applicators	Testis	21	1.1	(0.7-1.7)	Decreased incidence compared to an earlier study on the same cohort[137]
Faustini *et al* [52] 1993	Italy	Farmers	Prostate	8	0.9	(0.4-1.8)	Mortality study followed 1972-88
Figà-Talamanca *et al* [53] 1993	Italy	Pesticide applicators	Prostate	6	0.9	(0.3-1.9)	Mortality study, provincial basis
					1.0	(0.4-2.2)	National basis
Firth *et al* [124] 1996	New Zealand	Farmers	Brain	95	1.4	(1.1-1.7)	Incidence study; no report on significance
			Lymphosarcoma	52	1.5	(1.1-1.9)	in farmers or pesticide applicators *re*
		Wood and protective service workers	Prostate	54	1.4	(1.1-1.9)	prostate cancer
Flesch-Janys *et al* [152] 1995	Germany	Workers in herbicide production	All	133	—	—	Mortality study. Exposure compared
		TCDD exposure			2.4	(1.8-3.3)	between highest and lowest decile in a
		PCDD/F exposure			3.3	(2.1-5.3)	cohort of 1,189 male workers

Continued

Table 5. Continued

Publication (ref.) Year	Location	Study population	Cancer site[a]	No. of cases	RR[b]	(CI)[c]	Comments
Kogevinas *et al*[154] 1993	International cohort	701 women	All	29	1.0	(0.6-1.4)	Incidence study. The cohort is taken from an international register of workers, employed in production (n = 699) or spraying (n = 2)
			Breast	7	0.9	(0.4-1.9)	
		TCDD exposure	All	9	2 2	(1 0-4.2)	
		Probable	Breast	1	0 9	(0 0-4.8)	
			All	20	0 8	(0.5-1.2)	
		Unlikely	Breast	6	0.9	(0.3-2.0)	
			STS	0	0.2	—	
			NHL	0	0.4	—	
Kristensen *et al*[155] 1996	Norway	Farmers	Prostate	277	1.0	(0.9-1 1)	Incidence study
Morrison *et al*[134] 1993	Canada	Farmers, herbicide spraying	Prostate	127	2.2	(1.3-3.8)	$P < 0.01$ for farmers spraying more than 250 acres[d] with herbicides, otherwise no relation
		Also aged 45 years or more		20	1.2	(1.0-1.5)	Herbicide spraying more than 250 acres *cf* 0 acres
Morrison *et al*[99] 1994	Canada	Operators on farms	NHL				Estimated RR from a Poisson regression analysis of mortality 1971-87
							Acres[d] sprayed with herbicides in1970:
				54	1.0	—	0
				19	1.3	(0.8-2.3)	1-99
				29	1 2	(0.7-1.9)	100-249
				15	1.0	(0.5-1.7)	250+
							Also restricted to farmers appearing on both the 1971 and 1981 census of agriculture
							Acres sprayed with herbicides in 1970:
				21	1 0	—	0
				11	1.2	(0.6-2.6)	1-159
				8	0.9	(0.4-2.0)	160-379
				19	2.1	(1.1-3.9)	380+

Continued

Table 5. Continued

Publication (ref.) Year	Location	Study population	Cancer site[a]	No. of cases	RR[b]	(CI)[c]	Comments
Morrison *et al*[156] 1995	Canada	Fruit and vegetable farmers, farm operators	All				Mortality study; farmers classified based on numbers of acres planted and numbers of fruit trees:
			Brain	4	0.7	(0.2-1.9)	> 10 acres in vegetables
				61	1 5	(1.1-1.9)	> 10-50 acres in corn
				19	1.2	(0 4-1.3)	> 50 acres in corn
				19	1.1	(0.7-1.7)	25+ fruit trees
			NHL	6	1.1	(0.4-2.3)	> 10 acres in vegetables
				65	1.4	(1.1-1.8)	> 10-50 acres in corn
				13	0.8	(0.7-1.8)	> 50 acres in corn
				12	0.5	(0 3-1.0)	25+ fruit trees
			HD	2	1.9	(0.2-6.8)	> 10 acres in vegetables
				12	1.5	(0.8-2.5)	> 10-50 acres in corn
				2	0.6	(0.4-1.3)	> 50 acres in corn
				5	1.4	(0.5-3.3)	25+ fruit trees
			Multiple myeloma	3	1.0	(0.2-3.0)	> 10 acres in vegetables
				24	1 0	(0 6-1.5)	> 10-50 acres in corn
				10	1.2	(0.1-2.2)	> 50 acres in corn
				11	0.9	(0.4-1.6)	25+ fruit trees
Pukkala *et al*[128] 1997	Finland	120,000 male and 85,000 female farmers	All				Incidence study
			Male	11,499	0.8	(0.8-0.8)	
			Female	5,266	0.8	(0.8-0.9)	
			Lung	2,460	0.7	(0.7-0 7)	
				141	0.5	(0.5-0.6)	
			NHL	256	0.9	(0.8-1.0)	
				129	0.9	(0.8-1.1)	
			HD	85	1.4	(1.1-1.7)	
				20	0.8	(0.5-1.2)	
				24	1.7	(1.1-2.6)	Farms without animals
			Multiple myeloma	174	1.0	(0.8-1.1)	
				76	0.9	(0 7-1.2)	
			Leukemia	317	1 0	(0.9-1.1)	
				112	1.0	(0.8-1.1)	
			Prostate	2,212	1.0	(0.9-1.0)	
			Testis	36	0.9	(0.7-1.3)	
			Breast	11	0.7	(0.4-1.3)	
				1,474	0.8	(0.7-0.8)	
			Malignant melanoma	330	1.1	(1.0-1.2)	
				156	1 0	(0.8-1.1)	
			Other skin	400	1.1	(1.0-1.2)	
				133	1.1	(0.9-1.2)	

Continued

Table 5. Continued

Publication (ref.) Year	Location	Study population	Cancer site[a]	No. of cases	RR[b]	(CI)[c]	Comments
Ronco *et al*[127] 1992	Denmark	Farmers	Lung	559	0.4[e]	—	Incidence study
		self-employed, employees		191	0.7[e]	—	
			NHL	120	1 0	—	
				27	1.0	—	
			HD	27	0 6[e]	—	
				13	1.0	—	
			Multiple myeloma	63	1.0	—	
				20	1.6[e]	—	
			Leukemia	145	0.9	—	
				33	1.0	—	
			Prostate	399	0 9[e]	—	
				63	0.8[e]	—	
			Testis	74	0.9	—	
				23	0 6[e]	—	
			Skin	493	0 7[e]	—	
				98	0.7[e]	—	
			Lung	111	0.5[e]		
	Italy	Farmers		67	0.7[e]	—	Mortality study
		self-employed, employees		9	1.3	—	
			NHL	5	1.3	—	
				10	2.3[e]	—	
			HD	1	0.3	—	
				12	0.7	—	
			Leukemia	8	0.9	—	
Semenciw *et al*[157] 1993	Canada	156,242 prairie farmers	Multiple myeloma				Mortality study 1971-87
				77	1.0	—	0 acres sprayed
				26	1.1	(0.7-1.8)	1-99
				34	1.1	(0.7-1.7)	100-249
				23	1.3	(0.8-2.1)	250+ acres sprayed
Semenciw *et al*[126] 1994	Canada	156,242 prairie farmers	All	8,411	0.8	(0.8-0.8)	Mortality study 1971-87.
			NHL	253	0 8	(0.7-0 9)	No association was observed between
			HD	34	0.8	(0.5-1.1)	leukemia mortality and use of either
			Multiple myeloma	160	0.8	(0.7-1 0)	insecticides or herbicides
			Leukemia	357	0 9	(0.8-1 0)	
		Herbicide spraying	Leukemia	185	1.0	—	0 acres sprayed
				42	1.0	(0.7-1.4)	250+ acres sprayed
		Insecticide spraying	Leukemia	345	1.0	—	0 acres sprayed
				7	1.1	(0.5-2.3)	90+ acres sprayed

Continued

Table 5. Continued

Publication (ref.) Year	Location	Study population	Cancer site[a]	No. of cases	RR[b]	(CI)[c]	Comments
Torchio *et al* [158] 1994	Italy	> 130 poultry 23,401 pesticide applicators	All	770	0.6	(0.6-0.6)	Mortality study
			Lung	155	0.5	(0.4-0.5)	
			HD	11	1.0	(0.5-1.7)	
			Multiple myeloma	5	0.4	(0.1-1.0)	
			Leukemia	27	0.8	(0.5-1.1)	
			Prostate	66	1.0	(0.7-1.2)	
Wiklund *et al* [54] 1994	Sweden	Female farmers	All	4,474	0.9	(0.8-0.9)	Incidence study divided in geographic regions and age groups
			Breast	1,159	0.8	(0.8-0.9)	
			Cervix uteri	75	0.4	(0.3-0.5)	
			STS	21	0.6	(0.4-1.0)	
			NHL	94	0 8	(0.6-1.0)	
			HD	25	1 1	(0.7-1.7)	
			Multiple myeloma	73	1.1	(0.9-1.4)	
			Leukemia	112	0.9	(0.8-1.1)	
			Lung	94	0.5	(0.4-0.5)	
			Brain (Nervous system)	189	1.1	(0.9-1.2)	
Wiklund *et al* [55] 1995	Sweden	Male farmers	All	15,040	0.8	(0.8-0.8)	Incidence study divided in geographic regions and age groups
			Lung	783	0.4	(0.3-0.4)	
			STS	121	1.0	(0.8-1.2)	
			NHL	508	1.0	(0.9-1.1)	
			HD	111	1 0	(0.8-1.2)	
			Multiple myeloma	355	1.2	(1.1-1.4)	
			Leukemia	583	1.0	(0.9-1.1)	
			Skin	676	1.0	(0.9-1.1)	
			Prostate	3,987	0.9	(0.9-1.0)	
			Testis	67	1.0	(0.7-1.2)	

Continued

Table 5. Continued

Publication (ref.) Year	Location	Study population	Cancer site[a]	No. of cases	RR[b]	(CI)[c]	Comments
Zhong and Ransson[159] 1996	Iceland	2,449 licensed pesticide applicators 21,547 person years	All Male Female Female and male Lung Male NHL Male Female and male Leukemia Male Female and male Prostate Testis Malignant melanoma Other skin	 59 12 71 5 2 3 2 3 10 2 1 5	 0.8 0.7 0.8 0.5 1.1 1.5 1.3 1.7 0.7 1 2 1.2 2.8	 (0 6-1.1) (0.4-1.3) (0 6-1.0) (0.2-1.2) — — — — (0.3-1.3) — — (0.9-6.6)	Incidence study

[a] Abbreviations: NHL = non-Hodgkin's lymphoma; HD = Hodgkin's disease; STS = soft tissue sarcoma
[b] RR = relative risks including SMR (standardized mortality ratios) and SIR (standardized incidence ratios), *etc.*
[c] CI = 95 percent confidence interval.
[d] 1 acre = 0.405 hectares.
[e] Statistically significant at $P < 0.05$.

group. In older studies, some cases of NHL may have been misclassified as Hodgkin's disease.[107] Both Hodgkin's disease and NHL comprise a heterogenous group of malignancies. The majority of NHLs are of B-cell origin, but some are closer to Hodgkin's disease and are of T-cell origin.[107,162] Further misclassification might arise due to the ambiguous borderline between lymphoblastic NHL and acute lymphoblastic leukemia.[163-165] Histopathologic review of Hodgkin's disease cases has entailed reclassification to NHL in up to 40 percent.[166,167] Misclassification of disease may explain some of the different results among studies of similar design.

Impurities in the phenoxy acid herbicides have changed over time, possibly an important factor when evaluating studies. Organochlorine compounds – *e.g.*, chlorophenols and dioxins (TCDD) – have been rather common in older formulations of, for example, phenoxy acid herbicides, particularly 2,4-D and 2,4,5-T. The latter was therefore withdrawn in most countries during the 1970s or early 1980s.

A causal association between exposure to pesticides and risk of NHL is supported by G-banded chromosome analyses of peripheral blood from pesticide applicators with mixed pesticide exposure. Significantly increased rearrangement-frequencies were found in the pesticide applicators compared with unexposed control subjects. Of particular interest with regard to lymphoma risk was the excess rearrangements and breaks involving bands 14q32 and 18q21, which are the most common.[168]

The possibility of confounding by ultraviolet radiation (UVR) recently has been proposed. An association between the incidence of NHL and solar UVR was reported from Denmark and Sweden[169] and from the UK[170] but not in another study from the US.[171] There was an excess risk of more than 30 percent for counties in the highest compared with the lowest quartiles of solar UVR, after adjustment for social class and employment in agriculture; the study is, however, based on ecological correlation. Another study supports recent suggestions that UVR-induced impairment of immune functioning contributes to the etiology of NHL.[172] There clearly is need for further research on individual exposure to pesticides and solar radiation before a conclusion can be drawn.

Organochlorine compounds

Two recently published reviews[1,49] evaluate organochlorine compounds and the risk of estrogen-related cancers in women. For example, the most toxic dioxin, 2,3,7,8-TCDD, has antiestrogenic properties, while one DDT compound – o, p'-DDT – is weakly estrogenic.[1] The authors conclude that available data do not indicate that organochlorine compounds – including DDT, methoxychlor, chlordecone, lindane, and contaminants in pesticides such as polychlorinated dibenzo-*p*-dioxins (PCDD), and polychlorinated dibenzofurans (PCDF) – have sufficient estrogenic activity to affect the risk of either breast cancer or endometrial cancer in any but the most unusual situation.

Farming and pesticides

Farming entailing exposure to different pesticides has been associated with increased risk to other cancer sites. For example, some, but not all, studies on the risk of prostate cancer in farmers indicate increased risk. The etiology of this common malignancy is still unclear. While the DDT-metabolite p,p'-DDE blocks the androgen receptor in rats,[173] the relevance of this finding to human prostate cancer remains to be established. The apparent association between pesticides and multiple myeloma may be due to confounding by domestic animals and zoonotic viruses.[21,24,55,65,76]

The few existing studies on the risk of testicular cancer following exposure to unspecified[131,134] or specific[174] pesticides do not permit any conclusion. It has been suggested that the risk of testicular cancer may increase as a result of high estrogen exposure *in utero* caused by, for example, dietary habits, use of synthetic estrogens, or environmental estrogenic chemicals.[174] However, no ecologic correlation was found between mean p,p'-DDE levels in human breast milk and incidence of testicular cancer in Scandinavia.[175] Taken together, the evidence of an association is not strong, but it remains important to consider exposure to pesticides in future studies of testicular cancer.

Conclusion

During the last decade, well-designed, long-term studies of some old pesticides show no carcinogenicity in animals. Some pesticides which are animal carcinogens, such as captafol, chlordane, DDT, dichlorvos, and organomercury compounds have been withdrawn from the market in several countries. There is, however, need for caution and warning because some of them are still exported to developing countries with insufficient protection from occupational pesticide exposure. Epidemiologic studies provide some, albeit usually limited, support of an association between exposure to pesticides – mostly insecticides of organochlorine origin and phenoxy acid herbicides – and risk of cancer. There is a need for cohort studies with detailed information on individual exposure to pesticides, and for evaluation of rare tumors in case-control studies. Studies on exposure to pesticides in homes, and lawn and garden treatment also are needed, because of their increased use both in the US and in many European countries. Finally, due to lack of knowledge

about long-term effects of many pesticides, use of protective clothing and following instructions remain important when handling pesticides.

Acknowledgment — This review was written in memory of Professor Ulf G. Ahlborg who initiated the work.

References

1. Ahlborg UG, Lipworth L, Titus-Ernstoff L, *et al.* Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: An assessment of the biological and epidemiological evidence. *Crit Rev Toxicol* 1995; 25: 463-531.
2. Axelson O. Pesticides and cancer risks in agriculture. *Med Oncol Tumor Pharmacother* 1987; 4. 207-17.
3. Blair A, Malker H, Cantor KP, Burmeister L, Wiklund K. Cancer among farmers. A review. *Scand J Work Environ Health* 1985; 11: 397-407.
4. Blair A, Axelson O, Franklin C, *et al.* Carcinogenic effects of pesticides. In: Baler SR, Wilkinson CF, eds. *The Effects of Pesticides in Human Health* Princeton, NJ (USA): Princeton Scientific Pub Co., 1990: *Advances in Modern Environmental Toxicology, Vol XVIII.* 201-60.
5. Blair A, Zahm SH. Cancer among farmers. *Occup Med State Art Rev* 1991; 6: 335-54.
6. Bond GG, Bodner KM, Cook RR. Phenoxy herbicides and cancer: Insufficient epidemiologic evidence for a causal relationship. *Fund Appl Toxicol* 1989; 12: 172-88.
7. Food and Agriculture Organization of the United Nations. FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. Published in FAO plant production and protection papers, *e.g.*, Pesticide residues in food 1993; No 122. Rome, Italy, 1993
8. Flanders DW. Review: Prostate cancer epidemiology. *Prostate* 1984, 5: 621-9.
9. Hardell L, Eriksson M, Axelson O, Zahm SH Cancer epidemiology. (Chapter 16) In: Schecter A, ed. *Dioxins and Health* New York, NY (USA): Plenum Press, 1994. 525-47.
10. International Agency for Research on Cancer. *Miscellaneous Pesticides.* Lyon, France: IARC, 1983; *IARC Monogr Eval Carcinog Risks Humans,* Vol. 30.
11. International Agency for Research on Cancer. *Some Halogenated Hydrocarbons and Pesticide Exposures.* Lyon, France: IARC, 1986; *IARC Monogr Eval Carcinog Risks Humans,* Vol. 41.
12. International Agency for Research on Cancer *Overall Evaluations of Carcinogenicity: An Updating of IARC* Monographs Volumes 1 to 42. Lyon, France: IARC, 1987, *IARC Monogr Eval Carcinog Risks Humans,* Supplement 7.
13. International Agency for Research on Cancer. *DDT and Associated Compounds (Review). Occupational Exposures in Insecticide Application, and Some Pesticides.* Lyon, France: IARC, 1991; *IARC Monogr Eval Carcinog Risks Humans,* Vol. 53: 179-249.
14. International Agency for Research on Cancer. *Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry.* Lyon, France IARC, 1993; *IARC Monogr Eval Carcinog Risks Humans,* Vol. 58: 119-237.
15. International Agency for Research on Cancer. *Some Industrial Chemicals.* Lyon, France: IARC, 1994; *IARC Monogr Eval Carcinog Risks Humans,* Vol. 60.
16. International Agency for Research on Cancer. *Wood Dust and Formaldehyde.* Lyon, France: IARC, 1995; *IARC Monogr Eval Carcinog Risks Humans,* Vol. 62.
17. International Agency for Research on Cancer. *Occupational Cancer in Developing Countries.* Lyon, France, 1994; IARC Sci. Pub. No. 129.
18. Kogevinas M, Saracci R, Winkelmann R, *et al.* Cancer incidence and mortality in women occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins *Cancer Causes Control* 1994; 4: 547-53.
19. Kogevinas M, Boffetta P, Pearce N. Occupational exposure to carcinogens in developing countries. (Chapter 5) In: Pearce N, Matos E, Vainio H, Boffetta P, Kogevinas M, eds. *Occupational Cancer in Developing Countries.* Lyon, France. International Agency for Research on Cancer, 1994, IARC Sci. Pub No. 129: 63-95 (ref. 17).
20. Lipworth L. Review. Epidemiology of breast cancer. *Eur J Cancer Prev* 1995; 4: 7-30.
21. Maroni M, Fait A. Health effects in man from long-term exposure to pesticides. A review of the 1975-1991 literature. International Centre for Pesticide Safety. *Toxicology* 1993; 78. 1-104, 151-74.
22. McDuffie HH. Women at work: Agriculture and pesticides. *JOM* 1994; 36: 1240-6.
23. Morrison HI, Wilkins K, Semenciw R, Mao Y, Wigle D. Review. Herbicides and cancer. *JNCI* 1992; 84 1866-74.
24. Pearce N, Reif JS. Epidemiologic studies of cancer in agricultural workers. *Am J Ind Med* 1990; 18: 133-48.
25. Schecter A, ed. *Dioxins and Health.* New York, NY (USA): Plenum Press, 1994.
26. Sterling TD, Arundel AV. Health effects of phenoxy herbicides. A review. *Scand J Work Environ Health* 1986; 12. 161-73.
27. Swedish National Chemicals Inspectorate, Swedish Environmental Protection Agency. *Alternatives to Persistent Organic Pollutants.* The Swedish input to the IFCPS expert meeting on persistent organic pollutants in Manila, The Philippines, 17–19 June 1996 Report 4/96. Swedish National Chemicals Inspectorate, Swedish Environmental Protection Agency. 1996.
28. Vainio H, Hesso A, Jäppinen P. Chlorinated dioxins and dibenzofurans in the environment — a hazard to public health? *Scand J Work Environ Health* 1989, 15: 377-82.
29. Vainio H, Matos E, Kogevinas M. Identification of occupational carcinogens. (Chapter 4) In Pearce N, Matos E, Vainio H, Boffetta P, Kogevinas M, eds. *Occupational Cancer in Developing Countries.* Lyon, France International Agency for Research on Cancer, 1994: IARC Sci. Pub. No. 129: 41-59 (ref. 17).
30. WHO-EHC (World Health Organization – Environmental Health Criteria series) (ICPS, International Programme on Chemical Safety). *Mercury; DDT and its Derivates; Arsenic; 2,4-Dichlorophenoxyacetic acid (2,4-D),* Geneva, Switzerland: WHO, Series from 1976-.
31. Zahm SH, Blair A *Carcinogenic Risks From Pesticides.* Philadelphia, PA (USA): JB Lippincott Co., 1993: 266-79; General Motors Cancer Research Foundation, Detroit, MI (USA).
32. Food and Agriculture Organization of the United Nations. *International Code of Conduct on the Distribution and Use of Pesticides.* Rome, Italy FAO, 1986: 28

33. Codex. Guide to Codex recommendations concerning pesticide residues. Part 1. General notes and guidelines. The Hague, Codex Alimentarius Commission (Report CAC/PRI-1984), 1984.
34. Council of Europe. Pesticides — advice and recommendations to be used by national and other authorities as well as manufacturers concerned with the registration of agricultural and non-agricultural pesticides, 6th ed. Strassbourg, 1984: 120.
35. World Health Organization and United Nation's Environment Programme (WHO and UNEP). *Public Health Impact of Pesticides Used in Agriculture*. Geneva, Switzerland: WHO, 1990; ISBN 92 4 156139 4.
36. Hassall KA. *The Chemistry of Pesticides: Their Metabolism, Mode of Action and Uses in Crop Protection*. Weinheim, Germany: Verlag Chemie, 1982.
37. Wood McKenzie. *Agrochemical Monitor, No. 50* London, UK: Wood McKenzie & Co. Ltd., 1987: 19
38. Brouwer FM, Terluin IJ, Godeschalk FE. Pesticides in the EC April 1994. The Hague, The Netherlands: Onderzoekverslag 121 Agricultural Economics Research Institute (LEI-DLO), 1994.
39. Oskam AJ, van Zeijts H, Thijssen GJ, Wossink GAA, Vijftigschild R. Pesticide use and pesticide policy in the Netherlands. An economic analysis of regulatory levies in agriculture. Wageningen, The Netherlands: Wageningen Agricultural University 1992.
40. Edwards CA. Pesticides as environmental pollutants. *In*: Ekström G, ed. *World Directory of Pesticide Control Organisations*. Trowbridge, Wiltshire (UK): Redwood Books Ltd,Crop protection publications UK. 1994: 1-23
41 Aspelin AL, Grube AH, Torla R. Pesticide industry sales and usage, 1990 and 1991. Market estimates Washington, DC: Environmental Protection Agency Report, 1992: 1-7.
42. Salem H, Olajos EJ. Review of pesticides: chemistry, uses and toxicology. *Toxicol Ind Health* 1988; 4: 291-321.
43. Jaenson TGT. Alternatives to POP pesticides for control of arthropods of medical and veterinary importance *In*: Alternatives to persistent organic pollutants. The Swedish input to the IFCPS expert meeting on persistent organic pollutants in Manila, The Philippines, 17–19 June 1996. Report 4/96. Swedish National Chemicals Inspectorate, Swedish Environmental Protection Agency, 1996: 19-77.
44. Mórner J. Alternative to POP pesticides for the protection of plants and building constructions. *In*: Alternatives to persistent organic pollutants. The Swedish input to the IFCPS expert meeting on persistent organic pollutants in Manila, Philippines, 17–19 June 1996. Report 4/96. Swedish National Chemicals Inspectorate, Swedish Environmental Protection Agency, 1996: 79-115.
45. World Health Organization *Urban Vector and Pest Control*. Geneva, Switzerland: WHO, 1988; Eleventh report of the WHO Expert Committee on Vector Biology and Control, WHO Technical Report Series, No. 767.
46 Selkirk JK, Soward SM, eds Compendium of Abstracts from Long-Term Cancer Studies Reported by the National Toxicology Program of the National Institute of Environmental Health Sciences from 1976 to 1992 Bethesda, MD (USA): US Dept of Health and Human Services, 1993, *Environmental Health Perspectives Supplement (EHP), Suppl. 1*: 101
47. Innes JRM, Ulland BM, Valeria MG, *et al.* Bioassays of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note *JNCI* 1969, 42: 1101-14.
48 Tarjan R, Kemeny T. Multigeneration studies on DDT in mice. *Food Cosmet Toxicol* 1969; 7. 215-22.
49 Adami HO, Lipworth L, Titus-Ernstoff L, *et al.* Review. Organochlorine compounds and estrogen-related cancers in women. *Cancer Causes Control* 1995; 6: 551-66.
50. Wiklund K, Dich J, Holm LE, Eklund G. Risk of cancer in pesticide applicators in Swedish agriculture. *Br J Ind Med* 1989; 46: 809-14
51 Blair A, Dosemeci M, Heineman EF. Cancer and other causes of death among male and female farmers from twenty-three states. *Am J Ind Med* 1993; 23: 729-42.
52 Faustini A, Forastiere F, Dibetta L, Magliola EM, Perucci CA. Cohort study of mortality among farmers and agricultural workers. *Med Lav.* 1993; 84: 31-41.
53 Figá-Talamanca I, Mearelli I, Valente P, Bascherini S. Cancer mortality in a cohort of rural licensed pesticide users in the province of Rome. *Int J Epidemiol* 1993; 22: 579-83.
54 Wiklund K, Dich J. Cancer risks among female farmers in Sweden. *Cancer Causes Control* 1994; 5: 449-57.
55. Wiklund K, Dich J. Cancer risks among male farmers in Sweden. *Eur J Cancer Prev* 1995; 4: 81-90.
56. Dosemeci M, Hoover RN, Blair A, *et al.* Farming and prostate cancer among African–Americans in the southeastern United States (Brief communication). *JNCI* 1994, 86: 1718–9.
57. Davis DL, Blair A, Hoel DG. Agricultural exposures and cancer trends in developed countries. *Environ Health Perspect* 1992; 100: 39-44.
58. Reif J, Pearce N, Kawachi I, Fraser J. Soft-tissue sarcoma, non-Hodgkin's lymphoma and other cancers in New Zealand forestry workers. *Int J Cancer* 1989; 43: 49-54.
59. Cantor KP, Blair A. Farming and mortality from multiple myeloma: a case-control study with the use of death certificates. *JNCI* 1984; 72: 251-5.
60. Saftlas AF, Blair A, Cantor KP, Hanrahan L, Anderson HA. Cancer and other causes of death among Wisconsin farmers. *Am J Ind Med* 1987; 11: 119-29.
61. Burmeister LF, Everett GD, Van Lier SF, Isacson P. Selected cancer mortality and farm practices in Iowa. *Am J Epidemiol* 1983, 118: 72-7.
62. Linet MS, Malker HSR, McLaughlin JK, *et al.* Non-Hodgkin's lymphoma and occupation in Sweden: A registry based analysis. *Br J Ind Med* 1993; 50: 70-84.
63. Persson B. Occupational exposures and malignant lymphoma. Doctoral thesis, Department of Occupational and Environmental Medicine, Faculty of Health Sciences, Linköping University, Sweden, 1995; *Linkoping University Medical Dissertations*, No. 475, ISSN 0345-0082.
64 Milham S, Hesser JE. Hodgkin's disease in woodworkers. *Lancet* 1967; 2: 136-7.
65. Eriksson M, Karlsson M Occupational and other environmental factors and multiple myeloma: A population based case-control study. *Br J Ind Med* 1992; 49: 95-103.
66 Skov T, Lynge E. Non-Hodgkin's lymphoma and occupation in Denmark. *Scand J Soc Med* 1991; 19: 162-9
67. Zahm SH, Blair A. Pesticides and non-Hodgkin's lymphoma *Cancer Res* 1992; 52(Suppl): 5485-8.
68. Weisenburger DD. Epidemiology of non-Hodgkin's lymphoma. Recent findings regarding an emerging epidemic. *Ann Oncol* 1994; 5(Suppl 1): S19-24.
69 Hardell L, Sandström A. Case-control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols *Br J Cancer* 1979; 39: 711-7.

70 Wingren G, Fredrikson M, Noorlind Brage H, Nordenskjöld B, Axelson O. Soft tissue sarcoma and occupational exposures. *Cancer* 1990; 66: 806-11.

71. Franceschi S, Barbone F, Bidoli E, *et al.* Cancer risk in farmers: results from a multi-site case-control study in North-Eastern Italy. *Int J Cancer* 1993; 53: 740-5

72 Cantor KP. Farming and mortality from non-Hodgkin's lymphoma: A case-control study. *Int J Cancer* 1982, 29: 234-47.

73. Pearce NE, Smith AH, Fisher DO. Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer registry-based study. *Am J Epidemiol* 1985; 121: 225-37.

74. Brownson RC, Reif JS, Chang JC, Davis JR. Cancer risks among Missouri farmers *Cancer* 1989; 64. 2381-6.

75. Burmeister LF. Cancer in Iowa farmers: Recent results. *Am J Ind Med* 1990; 18· 295-301.

76. Amadori D, Nanni O, Falcini F, *et al.* Chronic lymphocytic leukaemias and non-Hodgkin's lymphomas by histological type in farming-animal breeding workers: a population case-control study based on job titles. *Occup Environ Med* 1995; 52: 374-9.

77. Balarajan R. Malignant lymphomas in agricultural and forestry workers in England and Wales. *Public Health* 1988; 102: 585-92.

78. Blair A, Zahm SH, Pearce NE, Heineman EF, Fraumeni JF Jr. Clues to cancer etiology from studies of farmers. *Scand J Work Environ Health* 1992; 18: 209-15.

79. Pottern LM, Brown LM, Lines MS, Blair A. Genetic susceptibility and occupational exposures in the etiology of leukemia and non-Hodgkin's lymphoma. Ninth International Symposium on Epidemiology in Occupational Health. Cincinnati, OH (USA); 1992.

80. Brown LM, Burmeister LF, Everett GD, Blair A. Pesticide exposures and multiple myeloma in Iowa men. *Cancer Causes Control* 1993; 4: 153-6.

81. Demers PA, Vaughan TL, Koepsell TD, *et al.* A case-control study of multiple myeloma and occupation. *Am J Ind Med* 1993; 23: 629-39.

82. Richardson S, Zittoun R, Bastuji-Garin S, *et al.* Occupational risk factors for acute leukaemia: A case-control study. *Int J Epidemiol* 1992, 21: 1063-73.

83. Keller JE, Howe HL. Case-control studies of cancer in Illinois farmers using data from the Illinois State Cancer Registry and the US Census of Agriculture. *Eur J Cancer* 1994; 30A: 469-73

84. Aronson KJ, Siemiatycki J, Dewar R, Gérin M. Occupational risk factors for prostate cancer: Results from a case-control study in Montréal, Québec, Canada. *Am J Epidemiol* 1996; 143: 363-73.

85. Andersson SO, Baron J, Bergström R, Lindgren C, Wolk A, Adami HO. Life-style factors and prostate cancer risk – a case–control study in Sweden *Cancer Epidemiol Biomark Prev* 1996, 5: 509-13.

86. Hardell L. Soft-tissue sarcomas and exposure to phenoxy acids: A clinical observation. *Lakartidningen* 1977; 74: 2753-4.

87. Eriksson M, Hardell L, Berg NO, Moller T, Axelson O Soft-tissue sarcomas and exposure to chemical substances A case-referent study. *Br J Ind Med* 1981, 38. 27-33.

88. Hardell L, Eriksson M. The association between soft-tissue sarcomas and exposure to phenoxyacetic acids. A new case-referent study. *Cancer* 1988; 62: 652-6.

89. Olsson H, Alvegård TA, Härkönen H, Brandt L, Möller T. Epidemiological studies on high-grade soft-tissue sarcoma within the framework of a randomised trial in Scandinavia. In: Alvegård TA. Management and Prognosis of Patients with High-Grade Soft-Tissue Sarcoma Doctoral thesis, University of Lund, Sweden, 1989.

90. Eriksson M, Hardell L, Adami HO. Exposure to dioxins as a risk factor for soft tissue sarcoma: A population based case-control study. *JNCI* 1990, 82: 486-90.

91. Kogevinas M, Kauppinen T, Winkelmann R, *et al.* Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins· Two nested case-control studies. *Epidemiology* 1995; 6: 396-402

92. Hardell L. Malignant lymphoma of histiocytic type and exposure to phenoxyacetic acids or chlorophenols. *Lancet* 1979; 1· 55-6

93. Hardell L, Eriksson M. Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case-control study. *Br J Cancer* 1981; 43: 169-76.

94. Olsson H, Brandt L. Non-Hodgkin's lymphoma of the skin and occupational exposure to herbicides. *Lancet* 1981 (b); 2: 579

95. Hoar SK, Blair A, Holmes FF, *et al.* Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA* 1986, 256: 1141-7.

96. La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Occupation and lymphoid neoplasms. *Br J Cancer* 1989; 60: 385-8.

97. Persson B, Dahlander AM, Fredriksson M, Noorlind Brage H, Ohlson CG, Axelson O Malignant lymphomas and occupational exposures. *Br J Ind Med* 1989; 46: 516-20.

98. Zahm SH, Weisenburger DD, Babbitt PA, *et al.* A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska *Epidemiology* 1990; 1: 349-56.

99. Morrison HI, Semenciw RM, Wilkins K, Mao Y, Wigle DT. Non-Hodgkin's lymphoma and agricultural practices in the prairie provinces of Canada. *Scand J Work Environ Health* 1994; 20: 42-7.

100. Hardell L, Eriksson M, Degerman A Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. *Cancer Res* 1994, 54 2386-9.

101. Zahm SH, Weisenburger DD, Saal RC, Vaught JB, Babbitt PA, Blair A The role of agricultural pesticide use in the development of non-Hodgkin's lymphoma in women. *Arch Environ Health* 1993, 48: 353-8

102. Donna A, Betta PG, Robutti F, Crosignani P, Berrino F, Bellingeri D Ovarian mesothelial tumors and herbicides· a case-control study. *Carcinogenesis* 1984, 5: 941-2.

103. Donna A, Crosignani P, Robutti F, *et al.* Triazine herbicides and ovarian epithelial neoplasms *Scand J Work Environ* 1989; 15 47-53.

104 Zahm SH, Weisenburger DD, Cantor KP, Holmes FF, Blair A. Role of the herbicide atrazine in the development of non-Hodgkin's lymphoma. *Scand J Work Environ Health* 1993; 19· 108-14.

105 Brown LM, Blair A, Gibson R, *et al* Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota *Cancer Res* 1990; 50: 6585-91.

106. Flodin U, Fredriksson M, Persson B, Axelson O. Chronic lymphatic leukemia and engine exhausts, fresh wood, and DDT: a case-referent study. *Br J Ind Med* 1988; 45: 33-8
107. Persson B, Fredriksson M, Olsen K, Boeryd B, Axelson O. Some occupational exposures as risk factors for malignant lymphomas. *Cancer* 1993; 72. 1773-8.
108. Falck F, Ricci A Jr, Wolff MS, Godbold J, Deckers P. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch Environ Health* 1992; 47: 143-6.
109. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. *JNCI* 1993; 85: 648-52.
110. Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. *JNCI* 1994; 86: 589-99
111. Hardell L, Bengtsson NO, Jonsson U, Eriksson S, Larsson LG. Aetiological aspects on primary liver cancer with special regard to alcohol, organic solvents and acute intermittent porphyria – An epidemiological investigation. *Br J Cancer* 1984; 50: 389-97.
112 Smith AH, Pearce NE, Fisher DO, Giles HJ, Teague CA, Howard JK. Soft tissue sarcoma and exposure to phenoxyherbicides and chlorophenols in New Zealand. *JNCI* 1984; 73: 1111-7.
113. Pearce NE, Smith AH, Howard JK, Sheppard RA, Giles HJ, Teague CA. Non-Hodgkin's lymphoma and exposure to phenoxyherbicides, chlorophenols, fencing work, and meat works employment: A case-control study. *Br J Ind Med* 1986; 43: 75-83.
114. Pearce NE, Sheppard RA, Smith AH, Teague CA. Non-Hodgkin's lymphoma and farming. An expanded case-control study. *Int J Cancer* 1987; 39: 155-61.
115. Cantor KP, Blair A, Everett G, *et al.* Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 1992; 52: 2447-55
116. Bertazzi PA, di Domenico A. Chemical, Environmental, and Health Aspects of the Seveso, Italy, Accident. (Chapter 18) In: Schecter A, ed. *Dioxins and Health*. New York, NY (USA): Plenum Press, 1994: 587-632.
117. Figgs LW, Dosemeci M, Blair A. United States Non-Hodgkin's lymphoma surveillance by occupation 1984–1989: a twenty-four state death certificate study *Am J Ind Med* 1995; 27: 817–35.
118. Hardell L. Phenoxy herbicides, chlorophenols, soft-tissue sarcoma (STS) and malignant lymphoma [Letter]. *Br J Cancer* 1993; 67: 1154-5
119. Heineman EF, Olsen JH, Pottern LM, Gomez M, Raffn E, Blair A. Occupational risk factors for multiple myeloma among Danish men. *Cancer Causes Control* 1992; 3: 555-68.
120. Pesatori AC, Consonni D, Tironi A, Zocchetti C, Fini A, Bertazzi A Cancer in a young population in a dioxin-contaminated area. *Int J Epidemiol* 1993; 22: 1010-3.
121. Pesatori AC, Sontag JM, Lubin JH, Consonni D, Blair A. Cohort mortality and nested case-control study of lung cancer among structural pest control workers in Florida (United States). *Cancer Causes Control* 1994; 5: 310-8.
122. Pottern LM, Heineman EF, Olsen JH, Raffn E, Blair A. Multiple myeloma among Danish women: employment history and workplace exposures *Cancer Causes Control* 1992; 3: 427-32.
123. Siemiatycki J, Dewar R, Nadon L, Gérin M. Occupational risk factors for bladder cancer: Results from a case-control study in Montreal, Quebec, Canada. *Am J Epidemiol* 1994, 140: 1061-80.
124. Firth HM, Cooke KR, Herbison GP Male cancer incidence by occupation: New Zealand, 1972-1984, *Int J Epidemiol* 1996, 25. 14-21.
125. Linet MS, McLaughlin JK, Malker HSR, *et al.* Occupational and hematopoietic and lymphoproliferative malignancies among women: A linked registry study. *J Occup Med* 1994; 11: 1187-98.
126. Semenciw RM, Morrison HI, Morison D, Mao Y. Leukemia mortality and farming in the prairie provinces of Canada *Can J Public Health* 1994, 85: 208-11.
127. Ronco G, Costa G, Lynge E. Cancer risk among Danish and Italian farmers. *Br J Ind Med* 1992; 49: 220-5.
128. Pukkala E, Notkola V. Cancer incidence among Finnish farmers, 1979-93. *Cancer Causes Control* 1997; 8: 25-33.
129. Viel JF, Richardson ST. Lymphoma, multiple myeloma and leukemia among French farmers in relation to pesticide exposure *Soc Sci Med* 1993; 37: 771-7.
130. Blair A, Grauman DJ, Lubia JH, Fraumeni JF Jr. Lung cancer and other causes of death among licensed pesticide applicators. *JNCI* 1983; 71: 31-7.
131. MacMahon B, Monson RR, Wang HH, Zheng T. A second follow-up of mortality in a cohort of pesticides applicators. *J Med* 1988; 30: 429-32.
132. Corrrao G, Calleri M, Carle F, Russo R, Bosia S, Piccioni P. Cancer risk in a cohort of licensed pesticide users *Scand J Work Environ Health* 1989; 15. 203-9.
133. Coggon D, Pannett B, Winter PD, Acheson ED, Bonsall J. Mortality of workers exposed to 2 methyl-4chlorophenoxy acetic acid. *Scand J Work Environ Health* 1986: 12: 448-54.
134. Morrison H, Savitz D, Semenciw R, *et al.* Farming and prostate cancer mortality. *Am J Epidemiol* 1993; 137: 270-80
135. Graham S, Gibson RW Social epidemiology of cancer of the testis. *Cancer* 1972, 29: 1242-9.
136. Mills PK, Newell GR, Johnson DE. Testicular cancer associated with employment in agriculture and oil and natural gas extraction. *Lancet* 1984; i. 207-10.
137. McDowall ME, Balarajan R. Testicular cancer mortality in England and Wales 1971-1980: variations by occupation *J Epidemiol Comm Health* 1986; 40: 26-9.
138. Wiklund K, Dich J, Holm LE. Testicular cancer among agricultural workers and pesticide applicators in Sweden *Scand J Work Environ Health* 1986, 12: 630-1.
139. Olsen JH, Jensen OM. Occupation and risk of cancer in Denmark an analysis of 93,810 cancer cases, 1970-1979. *Scand J Work Environ Health* 1987;13(Suppl 1): 1-91.
140. van den Eeden SK, Weiss NS, Strader CH, Daling JR. Occupation and the occurrence of testicular cancer. *Am J Ind Med* 1991;19:327-37
141 Dich J, Wiklund K, Holm LE. Testicular cancer in pesticide applicators in Swedish agriculture [Letter]. *Scand J Work Environ Health* 1996; 22: 66.
142. Alavanja MCR, Blair A, Masters MN. Cancer mortality in the US flour industry. *JNCI* 1990, 82: 840-8.
143 Lynge E A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. *Br J Cancer* 1985; 52. 259-70.
144 Fingerhut MA, Halperin WE, Marlow DA, *et al.* Cancer

mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N Engl J Med* 1991; 324: 212-8.
145. Lynge E. Cancer in phenoxy herbicide manufacturing workers in Denmark, 1947-87 – an update *Cancer Causes Control* 1993; 4: 261-72.
146. Delzell E, Grufferman S. Mortality among white and nonwhite farmers in North Carolina, 1976-1978. *Am J Epidemiol* 1985; 121: 391-402
147. Alavanja MCR, Blair A, Merkle S, Teske J, Eaton B Mortality among agricultural extension agents. *Am J Ind Med* 1988; 14: 167-76
148. Burmeister LF. Cancer mortality in Iowa farmers, 1971-1978. *JNCI* 1981; 66: 461-4.
149. Alavanja MCR, Blair A, Merkle S, Teske J, Eaton B, Reed B. Mortality among forest and soil conservationists. *Arch Environ Health* 1989; 44: 94-101.
150. Wigle DT, Semenciw RM, Wilkins K, *et al.* Mortality study of Canadian male farm operators. Non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. *JNCI* 1990; 82: 575-82.
151. Cantor KP, Booze CF. Mortality among aerial pesticide applicators and flight instructors: a reprint. *Arch Environ Health* 1991; 46: 110-6.
152 Flesch-Janys D, Berger J, Gurn P, *et al.* Exposure to polychlorinated dioxins and furans (PCDD/F) and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. *Am J Epidemiol* 1995; 142: 1165-75.
153. Alavanja MCR, Akland G, Baird D, *et al.* Cancer and non-cancer risk to women in agriculture and pest control: The agricultural health study. *J Occup Med* 1994; 36: 1247-50.
154. Kogevinas M, Saracci R, Winkelmann R, *et al* Cancer incidence and mortality in women occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins. *Cancer Causes Control* 1993, 4: 547-53.
155. Kristensen P, Andersen A, Irgens LM, Laake P, Bye AS. Incidence and risk factors of cancer among men and women in Norwegian agriculture. *Scand J Work Environ Health* 1996; 22:14-26.
156. Morrison HI, Semenciw RM, Morison D, Mao Y. Mortality among Canadian fruit and vegetable farmers In. Dosman J, ed. *Human Sustainability in Agriculture. Health, Safety, Sustainability.* Boca Raton, FL (USA): CRC Press Inc., 1995: 175–80.
157. Semenciw RM, Morrison HI, Riedel D, Wilkins K, Ritter L, Mao Y. Multiple myeloma mortality and agricultural practices in the prairie provinces of Canada. *JOM* 1993; 35: 557–61.
158. Torchio P, Lepore AR, Corrao G, *et al.* Mortality study on a cohort of Italian licensed pesticide users. *Sci Total Environ* 1994; 149. 183-91
159. Zhong Y, Ransson V. Cancer incidence among Icelandic pesticide users *Int J Epidemiol* 1996; 25: 1117-24.
160. Hernberg S. *Introduction to occupational epidemiology* Chelsea, UK: Lewis Publishers Inc , 1992.
161. Smith AH, Pearce NE. Update on soft tissue sarcoma and phenoxyherbicides in New Zealand. *Chemosphere* 1986; 15. 1795-8.
162. Chittal SM, Brousset P, Voigt JJ, Delsol G. Large B-cell lymphoma rich in T-cell simulating Hodgkin's disease *Histopathology* 1991; 19: 211-20
163. Harris NL, Jaffe ES, Stein H, *et al.* A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; 84: 1361-92.
164. Lennert K, Mohri N, Stein H, Kaiserling E. The histopathology of malignant lymphoma *Br J Haematol* 1975, 31(Suppl): 193-203.
165. Schaerer R, Lutz JM, Ménégoz F, Ferley JP, Swiercz P, Mousseau M. Lymphoma registration: Difficulties and results of a population-based registry. In: Sotto, Vrousos, Sotto, Vincent, eds. *Non-Hodgkin's Lymphomas. New Techniques and Treatments.* Basel, Switzeland: Karger, 1985; 4th Cancer Res Workshop, Grenoble, 1984: 6-12
166. Dige U, Johansson H, Lenner P, Norberg B, Roos G. Hodgkin's disease in northern Sweden 1971-1981 *Acta Oncol* 1991; 30: 593-6.
167. Martinsson U, Glimelius B, Sundström C. Lymphoma incidence in a Swedish county during 1969-1987. *Acta Oncol* 1992; 31: 275-82.
168. Garry VF, Tarone RE, Long L, Griffith J, Kelly JT, Burroughs B. Pesticide appliers with mixed pesticide exposure: G-banded analysis and possible relationship to non-Hodgkin's lymphoma. *Cancer Epidemiol Biomark Prev* 1996; 5: 11-6.
169. Adami J, Frisch M, Yuen J, Glimelius B, Melbye M. Evidence of an association between non-Hodgkin's lymphoma and skin cancer. *Br Med J* 1995, 310: 1491-5.
170. Bentham G. Association between incidence of non-Hodgkin's lymphoma and solar ultraviolet radiation in England and Wales. *Br Med J* 1996; 312. 1128-31.
171. Hartge P, Devesa SS, Grauman D, Fears TR, Fraumeni JF Jr. Non-Hodgkin's lymphoma and sunlight. *JNCI* 1996; 88: 298-300.
172 McMichael AJ, Giles GG. Have increases in solar ultraviolet exposure contributed to the rise in incidence of non-Hodgkin's lymphoma? *Br J Cancer* 1996; 73: 945-50.
173. Kelce WR, Stone CR, Laws SC, Gray LE, Kemppainen JA, Wilson EM. Persistent DDT metabolite p,p*-DDE is a potent androgen receptor antagonist [Letter]. *Nature* 1995; 375: 581-5.
174. Hayes RB, Brown LM, Pottern LM, *et al.* Occupation and risk for testicular cancer: A case-control study. *Int J Epidemiol* 1990, 19: 825-31.
175. Ekbom A, Wicklund-Glynn A, Adami HO. DDT and testicular cancer. *Lancet* 1996; 347: 553-4.